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Signed Stephen Hordley

Dated 26 September 2003

For official use

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P01/7700 0.00-0014046.7

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Notes
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The Patent Office

Request for grant of a Patent

Form 1/77

Patents Act 1977

1 Title of invention

1 Please give the title of the invention

COMPOUNDS USEFUL IN THERAPY

2 Applicant's details

☐ **First or only applicant**

2a If you are applying as a corporate body please give:

Corporate name
PFIZER LIMITED

Country *(and State of incorporation, if appropriate)*

UNITED KINGDOM

2b If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2c **In all cases,** please give the following details:

Address
RAMSGATE ROAD
SANDWICH
KENT

6892673001

UK postcode CT13 9NJ
(if applicable)

Country UNITED KINGDOM

ADP number
(if known)

2d, 2e and 2f:
If there are further applicants please provide details on a separate sheet of paper.

Second applicant (if any)

2d If you are applying as a corporate body please give:

Corporate name

Country *(and State of incorporation, if appropriate)*

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3
An address for service in the United Kingdom must be supplied.

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3 Address for service details

3a Have you appointed an agent to deal with your application?

Yes [X] No [ ] ➡ ***go to 3b***

⬇

Please give details below

Agent's name
J. R. HAYLES
Agent's address
PFIZER LIMITED
RAMSGATE ROAD
SANDWICH
KENT
Postcode CT13 9NJ 6409593002

Agent's ADP number

3b:
If you have appointed an agent, all correspondence concerning your application will be sent to the agent's United Kingdom address.

3b If you have not appointed an agent please give a name and address in the United Kingdom to which all correspondence will be sent:

Name

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ADP number
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4 Reference number

4 Agent's or applicant's reference number *(if applicable)*

5 Claiming an earlier application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

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Yes ☐ No ☒ ➡ ***go to 6***

⬇

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☐ and the Section of the Patents Act 1977 under which you are claiming:

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15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

6 Declaration of priority

6

If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number.

Please give the date in all number format, for example, 31/05/90 for 31 May 1990.

6 If you are declaring priority from previous application(s), please give:

Country of filing	Priority application number *(if known)*	Filing date *(day,month,year)*

7

The answer must be 'No' if:
- *any applicant is not an inventor*
- *there is an inventor who is not an applicant, or*
- *any applicant is a corporate body.*

8

Please supply duplicates of claim(s), abstract, description and drawing(s).

Please mark correct box(es)

9

You or your appointed agent (see Rule 90 of the Patents Rules 1990) must sign this request.

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A completed fee sheet should preferably accompany the fee.

7 Inventorship

7 Are you (the applicant or applicants) the sole inventor or the joint inventors?

Please mark the correct box

Yes ☐ No ☒ ➡

A statement of Inventorship on Patents Form 7/77 will need to be filed (see Rule 15).

8 Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77	—		
Claim(s)	2	Description	22
Abstract	—	Drawing(s)	1

8b Which of the following documents also accompanies the application?

Priority documents *(please state how many)*	
Translation(s) of Priority documents *(please state how many)*	
Patents Form 7/77 - Statement of Inventorship and Right to Grant *(please state how many)*	
Patents Form 9/77 - Preliminary Examination/Search	
Patents Form 10/77 - Request for Substantive Examination	

9 Request

I/We request the grant of a patent on the basis of this application.

Signed James Hayles Date 26/05/2000

(day month year)

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Compounds useful in therapy

This invention relates to compounds useful in the treatment or prevention of a variety of disorders, including those in which the modulation of CCR5 receptors is implicated. Disorders of interest include HIV and genetically related retroviral infections (and the resulting acquired immune deficiency syndrome, AIDS), and inflammatory diseases.

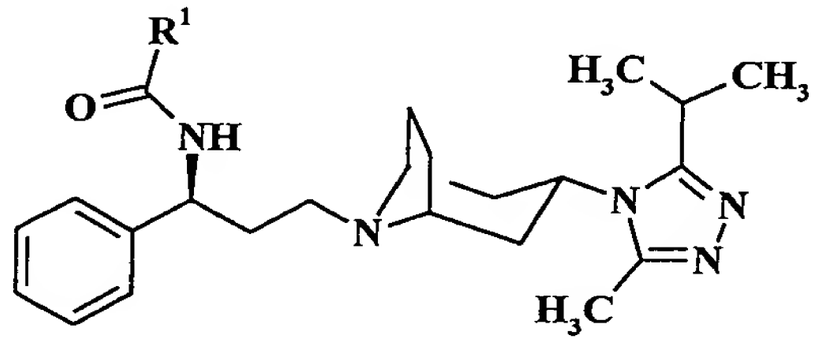
Without being limited by theory, the compounds of the present invention may be modulators, especially antagonists, of the activity of chemokine CCR5 receptors, particularly those which occur on the surfaces of certain cells within the human body. Modulators of CCR5 receptor may be useful in the treatment and prevention of various inflammatory diseases and conditions, and in the treatment and prevention of infection by HIV-1 and genetically related retroviruses. The name "chemokine", is a contraction of "chemotactic cytokines". The chemokines comprise a large family of proteins which have in common important structural features and which have the ability to attract leukocytes. As leukocyte chemotactic factors, chemokines play an indispensable role in the attraction of leukocytes to various tissues of the body, a process which is essential for both inflammation and the body's response to infection. Because chemokines and their receptors are central to the pathophysiology of inflammatory and infectious diseases, agents which are active in modulating, preferably antagonizing, the activity of chemokines and their receptors, are useful in the therapeutic treatment of such inflammatory and infectious diseases..

The chemokine receptor CCR5 is of particular importance in the context of treating inflammatory and infectious diseases. CCR5 is a receptor for chemokines, especially for the macrophage inflammatory proteins (MIP) designated MIP-1α and MIP-1β, and for a protein which is regulated upon activation and is normal T-cell expressed and secreted (RANTES).

There has been a substantial investigation of different classes of modulators of chemokine receptor activity, especially that of the CCR5 chemokine receptor. See for example

International Patent Application WO 98/25617 relating to substituted aryl piperazines as modulators of chemokine receptor activity.

According to the present invention, there is provided a compound of formula I,



I

wherein R^1 represents C_{3-6} cycloalkyl, or C_{1-6} alkyl substituted by one or more fluorine atoms;

or a pharmaceutically acceptable salt thereof.

The pharmaceutically acceptable salts of the compounds of formula I which contain a basic centre are, for example, non-toxic acid addition salts formed with inorganic acids such as hydrochloric, hydrobromic, sulphuric and phosphoric acid, with carboxylic acids, ammonia or with organo-sulphonic acids. Examples include the hydrochloride, hydrobromide, sulphate or bisulphate, phosphate or hydrogen phosphate, acetate, benzoate, succinate, fumarate, maleate, lactate, citrate, tartrate, gluconate, camsylate, ammonium, methanesulphonate, benzenesulphonate, and p-toluenesulphonate salts. For a review of suitable pharmaceutical salts see J. Pharm, Sci., 1977, 66, 1.

"Alkyl" in the definition of R^1 includes straight chain and branched groups.

The compounds of formula I may possess one or more chiral centres and so exist in a number of stereoisomeric forms. All stereoisomers and mixtures thereof are included in the scope of the present invention. Racemic compounds may either be separated using preparative HPLC and a column with a chiral stationary phase or resolved to yield individual enantiomers utilising methods known to those skilled in the art. In addition, chiral intermediate compounds may be resolved and used to prepare chiral compounds of formula I.

The compounds of formula I may exist in one or more tautomeric forms. All tautomers and mixtures thereof are included in the scope of the present invention.

The invention also includes radiolabelled compounds of formula I.

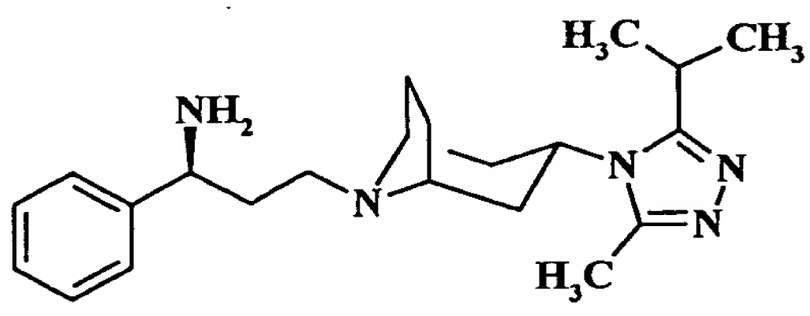
Preferred groups of compounds include those in which:

(a) R^1 represents C_{3-6} cycloalkyl (for example N-{(1*S*)-3-[*Exo*-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclobutanecarboxamide, or *N*-{(1*S*)-3-[*Exo*-3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclopentanecarboxamide; and

(b) R^1 comprises a trifluoromethyl group (for example N-{(1S)-3-[*Exo*-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}4,4,4-trifluorobutanamide.

The invention further provides a process for the production of a compound of formula I, or a pharmaceutically acceptable salt thereof, as defined above, which includes:

reacting a compound of formula II,



II

with a compound of formula III,

$$R^1CO_2H \qquad \text{III}$$

wherein R^1 is as defined above;

and where desired or necessary, converting the resulting compound into a pharmaceutically acceptable salt, or vice versa.

In the above process, the reaction is preferably carried out in the presence of a coupling agent (for example N-Benzyl-N'-cyclohexylcarbodiimide (which may be polymer-bound), or hydroxybenzotriazole hydrate and 1-(3-dimethylaminopropyl)-3-

ethylcarbodiimide methiodide), at or around room temperature, in a solvent that does not adversely affect the reaction (for example dichloromethane).

The preparation of the compounds of formula I, as defined above, is fully described in the accompanying Preparations and Examples.

The invention further provides the compound of formula II, as defined above. Compounds of formula III, as defined above, are either known or are available using known techniques.

The compounds of formula I, and their pharmaceutically acceptable salts, are useful because they have pharmacological activity in animals, including humans. More particularly, they are useful in the treatment or prevention of a disorder in which the modulation of CCR5 receptors is implicated. Disease states that may be mentioned include HIV, a retroviral infection genetically related to HIV, AIDS, or an inflammatory disease. The compounds of formula I, and their pharmaceutically acceptable salts, may be administered alone or as part of a combination therapy.

Thus, according to a further aspect of the invention, there is provided a compound of formula I, as defined above, or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.

There is further provided a pharmaceutical formulation containing a compound of formula I, as defined above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention also provides the use of a compound of formula I, as defined above, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prevention of a disorder in which the modulation of CCR5 receptors is implicated. The invention also provides the use of a compound of formula I, as defined above, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prevention of HIV, a retroviral infection genetically related to HIV,

AIDS, or an inflammatory disease. The invention also provides a method of treatment or prevention of these diseases, which comprises administering a therapeutically effective amount of a compound of formula I, as defined above, or a pharmaceutically acceptable salt thereof, to a patient in need of such treatment or prevention.

For human use the compounds of formula I, and their pharmaceutically acceptable salts, can be administered alone but will generally be administered in admixture with a suitable pharmaceutical excipient, diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

For example, the compounds of formula I, and their pharmaceutically acceptable salts, can be administered orally, buccally or sublingually in the form of tablets, capsules, ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for immediate-, delayed-, modified-, sustained-, pulsed- or controlled-release applications.

Such tablets may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate and glycine, disintegrants such as starch (preferably corn, potato or tapioca starch), sodium starch glycollate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the compounds of formula I, and their pharmaceutically acceptable salts, may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

The compounds of formula I, and their pharmaceutically acceptable salts, can also be administered parenterally, for example, intravenously, intra-arterially, intraperitoneally, intrathecally, intraventricularly, intraurethrally, intrasternally, intracranially, intramuscularly or subcutaneously, or they may be administered by infusion techniques. For such parenteral administration they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

The compounds of formula I, and their pharmaceutically acceptable salts, can also be administered intranasally or by inhalation and are conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray or nebulizer with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A [trade mark]) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA [trade mark]), carbon dioxide or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container, pump, spray or nebulizer may contain a solution or suspension of the active compound, e.g. using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of a compound of formula I, and their pharmaceutically acceptable salts, and a suitable powder base such as lactose or starch.

Alternatively, the compounds of formula I, and their pharmaceutically acceptable salts, can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a gel, hydrogel, lotion, solution, cream, ointment or dusting powder. The compounds of formula I, and their pharmaceutically acceptable salts, may also be dermally or transdermally administered, for example, by the use of a skin patch. They may also be administered by the pulmonary or rectal routes.

They may also be administered by the ocular route, particularly for treatment of the eye. For ophthalmic use, the compounds can be formulated as micronized suspensions in isotonic, pH adjusted, sterile saline, or, preferably, as solutions in isotonic, pH adjusted, sterile saline, optionally in combination with a preservative such as a benzylalkonium chloride. Alternatively, they may be formulated in an ointment such as petrolatum.

For application topically to the skin, the compounds of formula I, and their pharmaceutically acceptable salts, can be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, they can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

The compounds of formula I, and their pharmaceutically acceptable salts may also be used in combination with a cyclodextrin. Cyclodextrins are known to form inclusion and non-inclusion complexes with drug molecules. Formation of a drug-cyclodextrin complex may modify the solubility, dissolution rate, bioavailability and/or stability property of a drug molecule. Drug-cyclodextrin complexes are generally useful for most dosage forms and administration routes. As an alternative to direct complexation with the drug the cyclodextrin may be used as an auxiliary additive, e.g. as a carrier, diluent or solubiliser. Alpha-, beta- and gamma-cyclodextrins are most commonly used and suitable examples are described in WO-A-91/11172, WO-A-94/02518 and WO-A-98/55148.

For oral or parenteral administration to human patients the daily dosage levels of compounds of formula I, and their pharmaceutically acceptable salts, will be from 0.01 to 30 mg/kg (in single or divided doses) and preferably will be in the range 0.01 to 5 mg/kg. Thus tablets will contain 1mg to 0.4g of compound for administration singly or two or more at a time, as appropriate. The above dosages are, of course only exemplary of the

average case and there may be instances where higher or lower doses are merited, and such are within the scope of the invention.

Oral administration is preferred. Preferably, administration takes place shortly before an effect is required.

The compounds of formula I, and their pharmaceutically acceptable salts, have the advantage that they are more selective, have a more rapid onset of action, are more potent, are more stable, are more resistant to metabolism, or have other more desirable properties than the compounds of the prior art.

Included within the scope of the present invention are embodiments comprising coadministration of, and compositions which contain, in addition to a compound of the present invention as active ingredient, additional therapeutic agents and active ingredients. Such multiple drug regimens, often referred to as combination therapy, may be used in the treatment and prevention of any of the diseases or conditions mediated by or associated with CCR5 chemokine receptor modulation, particularly infection by human immunodeficiency virus, HIV. The use of such combinations of therapeutic agents is especially pertinent with respect to the treatment and prevention of infection and multiplication within a patient in need of treatment or one at risk of becoming such a patient, of the human immunodeficiency virus, HIV, and related pathogenic retroviruses. The ability of such retroviral pathogens to evolve within a relatively short period of time into strains resistant to any monotherapy which has been administered to said patient is well known in the technical literature.

In addition to the requirement of therapeutic efficacy which may necessitate the use of active agents in addition to the CCR5 chemokine receptor modulating compounds of formula I, and their pharmaceutically acceptable salts, there may be additional rationales which compel or highly recommend the use of combinations of drugs involving active ingredients which represent adjunct therapy, *i.e.*, which complement and supplement the function performed by the CCR5 chemokine receptor modulating compounds of the present invention. Such supplementary therapeutic agents used for the purpose of

auxiliary treatment include drugs which, instead of directly treating or preventing a disease or condition mediated by or associated with CCR5 chemokine receptor modulation, treat diseases or conditions which directly result from or indirectly accompany the basic or underlying CCR5 chemokine receptor modulated disease or condition. For example, where the basic CCR5 chemokine receptor modulated disease or condition is HIV infection and multiplication, it may be necessary or at least desirable to treat opportunistic infections, neoplasms, and other conditions which occur as the result of the immune-compromised state of the patient being treated. Other active agents may be used with the compounds of formula I, and their pharmaceutically acceptable salts, *e.g.*, in order to provide immune stimulation or to treat pain and inflammation which accompany the initial and fundamental HIV infection.

Thus, the methods of treatment and pharmaceutical compositions of the present invention may employ the compounds of formula I, and their pharmaceutically acceptable salts, in the form of monotherapy, but said methods and compositions may also be used in the form of multiple therapy in which one or more compounds of formula I, or their pharmaceutically acceptable salts, are coadministered in combination with one or more known therapeutic agents such as those described in detail further herein.

The utility of the compounds of formula I, and their pharmaceutically acceptable salts, as inhibitors of HIV infection may be demonstrated by any one or more methodologies known in the art, such as the HIV microculture assays described in Dimitrov *et al.*, *J. Clin. Microbiol.* **28**, 734-737 (1990)), and the pseudotyped HIV reporter assay described in Connor *et al.*, *Virology* **206** (2) 935-44 (1995).

The ability of the compounds of formula I, and their pharmaceutically acceptable salts, to modulate chemokine receptor activity is demonstrated by methodology known in the art, such as the assay for CCR5 binding following procedures disclosed in Combadiere *et al.*, *J. Leukoc. Biol.* **60**, 147-52 (1996); and/or intracellular calcium mobilisation assays as described by the same authors. Cell lines expressing the receptor of interest include those naturally expressing the receptor, such as PM-1, or IL-2 stimulated peripheral blood

lymphocytes (PBL), or a cell engineered to express a recombinant receptor, such as CHO, 300.19, L1.2 or HEK-293.

Preferred combinations of the present invention include simultaneous, or sequential treatments with a compound of formula I, or a pharmaceutically acceptable salt thereof, and one or more inhibitors of HIV protease and/or inhibitors of HIV reverse transcriptase, preferably selected from the class of non-nucleoside reverse transcriptase inhibitors (NNRTI), including but not limited to nevirapine, delavirdine, and efavirenz; from among the nucleoside/nucleotide inhibitors, including but not limited to zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, and adefovir dipivoxil; and from among the protease inhibitors, including but not limited to indinavir, ritonavir, saquinavir, nelfinavir, and amprenavir. Other agents useful in the above-described preferred embodiment combinations of the present invention include current and to-be-discovered investigational drugs from any of the above classes of inhibitors, including but not limited to FTC, PMPA, fozivudine tidoxil, talviraline, S-1153, MKC-442, MSC-204, MSH-372, DMP450, PNU-140690, ABT-378, and KNI-764. There is also included within the scope of the preferred embodiments of the present invention, combinations of a compound of formula I, or a pharmaceutically acceptable salt thereof, together with a supplementary therapeutic agent used for the purpose of auxiliary treatment, wherein said supplementary therapeutic agent comprises one or more members independently selected from the group consisting of proliferation inhibitors, *e.g.*, hydroxyurea; immunomodulators, *e.g.*, sargramostim, and various forms of interferon or interferon derivatives; fusion inhibitors, *e.g.*, AMD3100, T-20, PRO-542, AD-349, BB-10010 and other chemokine receptor agonists/antagonists; integrase inhibitors, *e.g.*, AR177; RNaseH inhibitors; inhibitors of viral transcription and RNA replication; and other agents that inhibit viral infection or improve the condition or outcome of HIV-infected individuals through different mechanisms.

Preferred methods of treatment of the present invention for the prevention of HIV infection, or treatment of aviremic and asymptomatic subjects potentially or effectively infected with HIV, include but are not limited to administration of a member independently selected from the group consisting of: (*i*) a compound within the scope of

Formula (I) as disclosed herein; (*ii*) one NNRTI in addition to a compound of (*i*); (*iii*) two NRTI in addition to a compound of (*i*); (*iv*) one NRTI in addition to the combination of (*ii*); and (*v*) a compound selected from the class of protease inhibitors used in place of an NRTI in combinations (*iii*) and (*iv*).

The preferred methods of the present invention for therapy of HIV-infected individuals with detectable viremia or abnormally low CD4 counts further include as a member to be selected: (*vi*) treatment according to (*i*) above in addition to the standard recommended initial regimens for the therapy of established HIV infections, *e.g.*, as described in Bartlett, J. G., "1998 Medical management of HIV infection", Johns Hopkins University publishers, ISBN 0-9244-2809-0. Such standard regimens include but are not limited to an agent from the class of protease inhibitors in combination with two NRTIs; and (*vii*) a standard recommended initial regimens for the therapy of established HIV infections, *e.g.*, as described in Bartlett, J. G., "1998 Medical management of HIV infection", Johns Hopkins University publishers, ISBN 0-9244-2809-0), where either the protease inhibitor component, or one or both of the NRTIs is/are replaced by a compound within the scope of Formula (I) as disclosed herein.

The preferred methods of the present invention for therapy of HIV-infected individuals that have failed antiviral therapy further include as a member to be selected: (*viii*) treatment according to (*i*) above, in addition to the standard recommended regimens for the therapy of such patients, *e.g.*, as described in Bartlett, J. G., "1998 Medical management of HIV infection", Johns Hopkins University publishers, ISBN 0-9244-2809-0); and (*ix*) a standard recommended initial regimens for the therapy of patients who have failed antiretroviral therapy, *e.g.*, as described in Bartlett, J. G., "1998 Medical management of HIV infection", Johns Hopkins University publishers, ISBN 0-9244-2809-0), where either one of the protease inhibitor components, or one or both of the NRTIs is/are replaced by a compound within the scope of Formula (I) as disclosed herein.

In the above-described preferred embodiment combinations of the present invention, the compound of Formula (I) and other therapeutic active agents may be administered in terms of dosage forms either separately or in conjunction with each other, and in terms of their time of administration, either serially or simultaneously. Thus, the administration of

one component agent may be prior to, concurrent with, or subsequent to the administration of the other component agent(s).

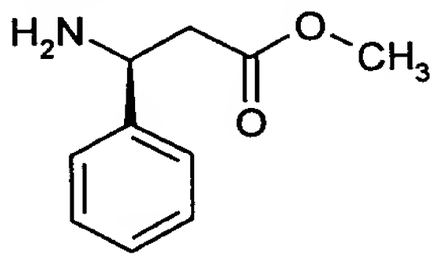
The compounds of this invention may be used for treatment of respiratory disorders, including: adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, rhinitis and chronic sinusitis.

The invention is illustrated by the following Preparations and Examples, in which the following abbreviations may be used:

0.88 ammonia	concentrated ammonium hydroxide solution, 0.88 SG
h	hour
min	minute
MS	mass spectrum
NMR	nuclear magnetic resonance

PREPARATION 1

Methyl (3*S*)-3-amino-3-phenylpropanoate



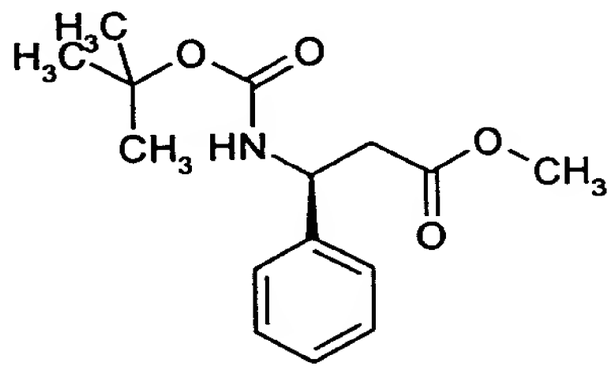
A solution of *tert*-butyl (3*S*)-3-amino-3-phenylpropanoate (5.04g, 22.9mmol) in 2.25M methanolic hydrochloric acid (100ml) was heated under reflux for 2 ½ hours. The mixture was cooled to room temperature, basified with saturated sodium carbonate solution to pH 8 and the phases separated. The aqueous layer was extracted with dichloromethane (4x). The combined organic solutions were washed with brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford the title compound, 3.97g.

^{1}H-NMR (400MHz, $CDCl_3$) : δ [ppm] 1.70 (2H, s), 2.66 (2H, d), 3.68 (3H, s), 4.43 (1H, t), 7.25-7.40 (5H, m).

LRMS: m/z 180.3 (MH^+).

PREPARATION 2

Methyl (3*S*)-3-[(*tert*-butoxycarbonyl)amino]-3-phenylpropanoate



The title compound from Preparation 1 (5.38g, 30mmol) and di-*tert*-butyl dicarbonate (8.72g, 40mmol) in tetrahydrofuran (50ml) and 2N sodium hydroxide solution (25ml) were stirred at room temperature for 2 hours. The reaction mixture was diluted with ethyl acetate, the layers

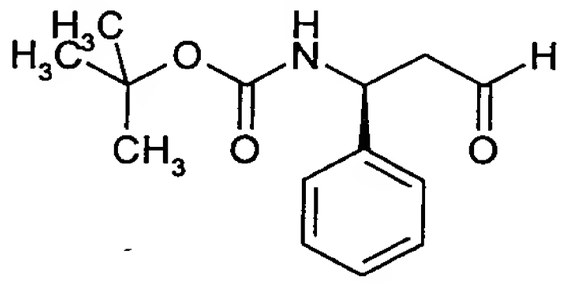
separated and the aqueous phase extracted with ethyl acetate (2x). The combined organic solutions were washed with water, brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford the title compound as a white solid, 8.39g.

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] 1.41 (9H, s), 2.84 (2H, m), 3.61 (3H, s), 5.10 (1H, bs), 5.41 (1H, bs), 7.22-7.36 (5H, m).

LRMS: m/z 279.7 (MH^+)

PREPARATION 3

tert-Butyl (1*S*)-3-oxo-1-phenylpropylcarbamate



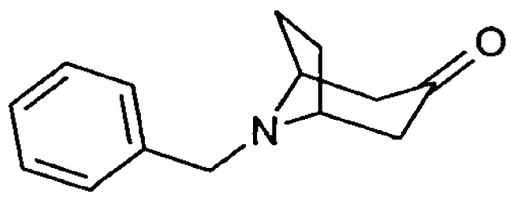
Diisobutylaluminium hydride (1M in dichloromethane, 60ml, 60mmol) was cooled to -78°C and added dropwise to a solution of the title compound from Preparation 2 (8.39g, 30mmol) in dichloromethane (150ml) at -78°C. The reaction was stirred for 90 minutes, then methanol (pre-cooled to -78°C, 40ml) was added. The mixture was allowed to warm to room temperature and poured into 2M hydrochloric acid (200ml). The layers were separated and the aqueous phase extracted with dichloromethane (2x). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford the title compound as a white solid, 6.72g.

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] 1.42 (9H, s), 2.86-3.00 (2H, m), 5.06 (1H, bs), 5.20 (1H, bs), 7.22-7.38 (5H, m), 9.75 (1H, s).

LRMS: m/z 250.1 (MH^+).

PREPARATION 4

8-Benzyl-8-azabicyclo[3.2.1]octan-3-one



A solution of 2,5-dimethoxytetrahydrofuran (50g, 378mmol) in 0.025M hydrochloric acid (160ml) was cooled to 0°C for 16 hours. Benzylamine hydrochloride (65g, 453mmol), ketomalonic acid (55g, 377mmol) and an aqueous solution of sodium acetate (300ml, 0.69M) were added and the reaction stirred at room temperature for 1 hour. The mixture was heated to 50°C for a further 90 minutes, then cooled in an ice bath and basified to pH12 with 2N

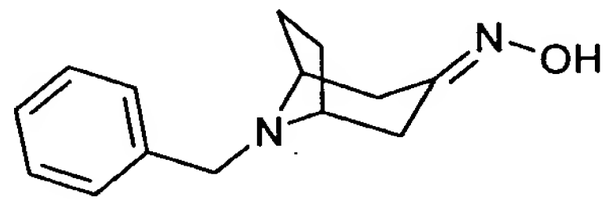
sodium hydroxide solution. The layers were separated, and the aqueous phase extracted with ethyl acetate (3x). The combined organic solutions were washed with water, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual brown oil was distilled under reduced pressure (126°C/3mm Hg) to afford the title compound as an off-white solid, 37.81g.

^1H NMR (400 MHz, $CDCl_3$): δ [ppm] 1.64 (2H, m), 2.06-2.14 (2H, m), 2.18 (1H, s), 2.23 (1H, s), 2.68 (1H, m), 2.72 (1H, m), 3.48 (2H, s), 3.73 (2H, s), 7.20-7.29 (1H, m), 7.32 (2H, m), 7.42 (2H, d).

LRMS: m/z 216.3 (MH^+).

PREPARATION 5

8-Benzyl-8-azabicyclo[3.2.1]octan-3-one oxime



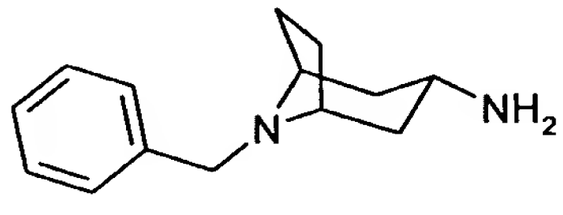
A mixture of the title compound from Preparation 4 (17.72g, 82mmol), hydroxylamine hydrochloride (5.72g, 82mmol) and pyridine (7.2ml, 89mmol), was heated under reflux in ethanol (500ml) for 20 hours. The reaction was allowed to cool to room temperature and diluted with saturated sodium carbonate solution. The mixture was filtered and the filtrate evaporated under reduced pressure. The residue was partitioned between dichloromethane and water, the layers separated and the aqueous layer extracted with dichloromethane (2x). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford the title compound as a pale brown solid, 18.10g.

^1H NMR (400 MHz, $CDCl_3$): δ [ppm] 1.45-1.56 (1H, m), 1.60-1.67 (1H, m), 1.96-2.07 (2H, bm), 2.12 (1H, m), 2.21 (1H, m), 2.57 (1H, m), 2.97 (1H, m), 3.32 (2H, m), 3.64 (2H, s), 7.06 (1H, s), 7.21-7.28 (1H, m), 7.32 (2H, m), 7.38 (2H, d).

LRMS: m/z 231.2 (MH^+)

PREPARATION 6

8-Benzyl-8-azabicyclo[3.2.1]octan-3-*exo*-amine



A solution of the title compound from Preparation 5 (18.10g, 79mmol) in pentanol (500ml) was heated under reflux. Sodium (22.0g, 957mmol) was added portionwise over 2.5 hours. The

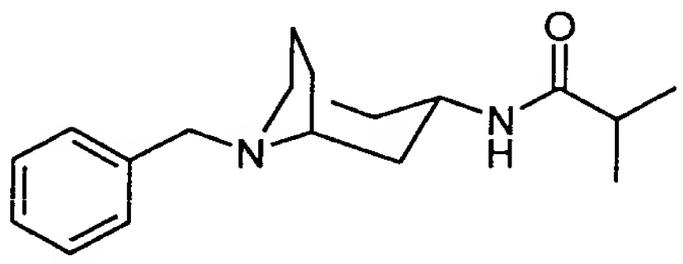
reaction was then heated under reflux for a further 2 hours, then cooled to 0°C in an ice bath. Water was added until no more hydrogen gas evolved. The mixture was acidified using 6N hydrochloric acid and the phases separated. The organic layer was extracted with 6N hydrochloric acid (3x), the combined aqueous extracts were basified to pH12 with sodium hydroxide pellets (400g) and the aqueous solution extracted with ethyl acetate (3x). The combined organic solutions were dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford the title compound, 15.65g.

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] 1.20-1.40 (2H, bm), 1.48 (2H, m), 1.58 (2H, d), 1.64-1.76 (2H, bm), 2.00 (2H, bm), 2.95 (1H, m), 3.19 (2H, bs), 3.57 (2H, s), 7.18-7.26 (1H, m), 7.30 (2H, m), 7.37 (2H, d).

LRMS: m/z 217.3 (MH^+).

PREPARATION 7

Exo-N-(8-benzyl-8-azabicyclo[3.2.1]oct-3-yl)-2-methylpropanamide



Triethylamine (9ml, 66.8mmol) was added to a solution of the title compound from Preparation 6 (13g, 60.1mmol), isobutyric acid (5.6ml, 60.5mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (11.6g, 60.4mmol) in dichloromethane (150ml). The reaction mixture was stirred at room temperature for 3 hours after which time more isobutyric acid (1.4ml, 15mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.9g, 15.1mmol) were added. The reaction mixture was stirred at room temperature for 2 days after which time more isobutyric acid (2.6ml, 28mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (5g, 26mmol) and triethylamine (3ml, 22.3mmol) were added. Saturated aqueous sodium carbonate solution (300ml) was added to the mixture and the product was extracted with dichloromethane (2x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using an elution gradient of dichloromethane: methanol: 0.88 ammonia (1:0:0 to 97:3:0.3) to afford the title compound as a white powder, 9.2g.

Found C, 75.43; H, 9.30; N, 9.82%

$C_{18}H_{26}N_2O$ requires C, 75.48; H, 9.15; N, 9.78%

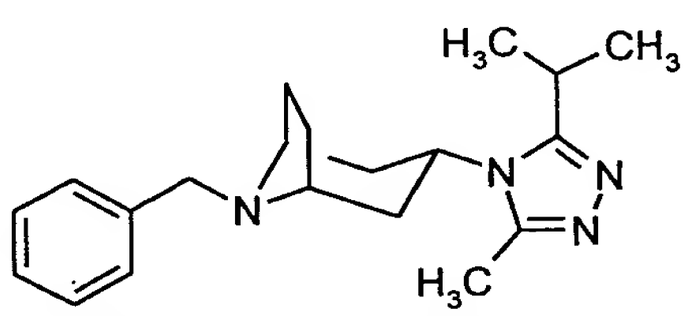
^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] 1.10 (6H, d), 1.47 (2H, tr), 1.60 (2H, s), 1.70 (2H, m), 1.80 (2H, m), 2.02 (2H, m), 2.27 (1H, m), 3.20 (2H, s), 4.10 (1H, m), 5.15 (1H, m), 7.20-7.40 (5H, m).

LRMS: m/z 287.4 (MH^+)

Melting point [°C]: 138-140

PREPARATION 8

Exo-8-benzyl-3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane



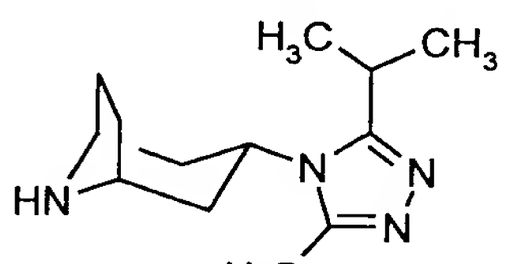
Phosphorus oxychloride (9ml, 96.9mmol) was added to a solution of the title compound from Preparation 7 (9.2g, 32mmol) and pyridine (16ml, 196mmol) in chloroform (20ml) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred at room temperature for 5 hours. The mixture was evaporated under reduced pressure. The residue was dissolved in chloroform (40ml) and acetic hydrazide (3.6g, 48.6mmol) was added. The mixture was heated at reflux for 3 hours. Saturated aqueous sodium carbonate solution (250ml) was added to the mixture and the product was extracted with dichloromethane (2x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure. Toluene (200ml) and *p*-toluenesulphonic acid monohydrate (100mg, 0.53mmol) were added to the residue. The reaction mixture was heated at reflux for 2 hours. The reaction mixture was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using an elution gradient of dichloromethane: methanol: 0.88 ammonia (1:0:0 to 95:5:0.5) to afford the crude product. The crude material was suspended in 6N hydrochloric acid (40ml) and heated at reflux for 12 hours after which time 12N hydrochloric acid (4ml) was added. The reaction mixture was heated at reflux for 2 hours. The mixture was evaporated under reduced pressure. The residue was basified by the addition of saturated aqueous potassium carbonate solution (200ml) and the product was extracted with dichloromethane (3x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using an elution gradient of dichloromethane: methanol: 0.88 ammonia (1:0:0 to 96:4:0.4) to afford the title compound as a white powder, 3.12g.

^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] 1.40 (6H, d), 1.70 (4H, m), 2.15-2.40 (4H, m), 2.60 (3H, s), 3.07 (1H, m), 3.37 (2H, s), 3.60 (2H, s), 4.30 (1H, m), 7.25-7.40 (5H, m).

LRMS: m/z 325.3(MH^+)

PREPARATION 9

Exo-3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane



Ammonium formate (6g, 92mmol) was added to a solution of the title compound from Preparation 8 (3.12g, 9.6mmol) and palladium hydroxide (500mg) in ethanol (400ml). The mixture was heated under reflux for 2 hours after which time 0.88 ammonia solution (2ml) was added. The mixture was heated under reflux for 1 hour and the reaction was allowed to cool to room temperature and filtered through Arbocel™ (filtration aid). The solvent was evaporated under reduced pressure to afford the title compound as a white solid, 1.91g

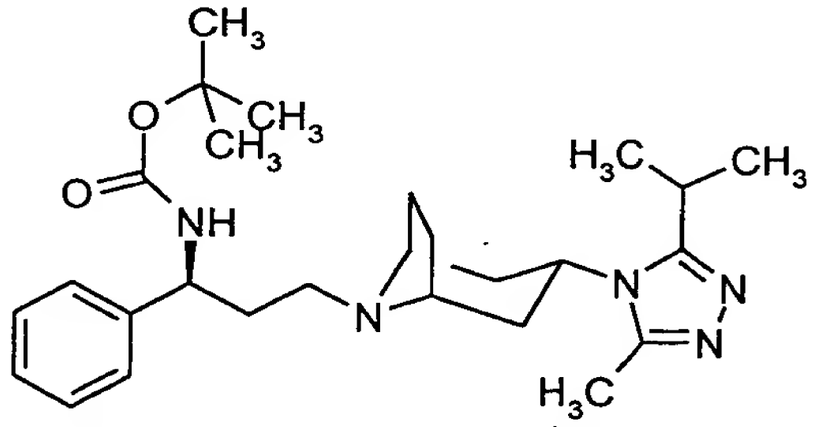
^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] 1.37 (6H, d), 1.70-2.25 (8H, m), 2.50 (3H, s), 3.05 (1H, m), 3.70 (2H, m), 4.32 (1H, m).

LRMS: m/z 235.0(MH^+)

Melting point [°C]: 150-154

PREPARATION 10

tert-Butyl (1*S*)-3-[3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropylcarbamate



Sodium triacetoxyborohydride (1.7g, 8.02mmol) and glacial acetic acid (1ml, 17.5mmol) were added to a solution of the title compound from Preparation 9 (1.6g, 6.84mmol) and the title compound from Preparation 3 (2g, 8.03mmol) in dichloromethane (40ml), and the reaction stirred at room temperature for 2 hours. The mixture was basified with 10% aqueous potassium carbonate solution, and extracted with dichloromethane (2x). The combined

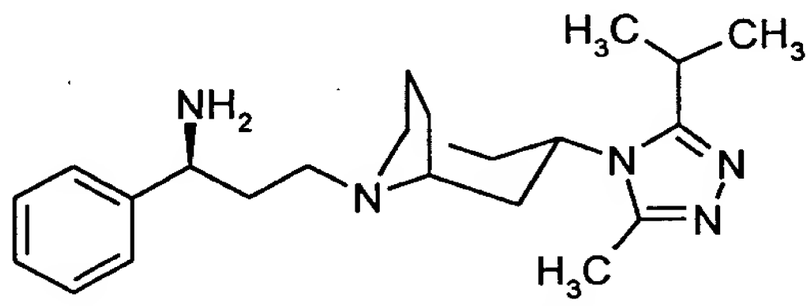
organic extracts were washed with brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using an elution gradient of dichloromethane: methanol: 0.88 ammonia (1:0:0 to 97.5:2.5:0.25) to afford the title compound as a white foam, 2.5g

^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] 1.40 (15H, m), 1.70 (4H, m), 1.80-2.15 (4H, m), 2.30 (2H, m), 2.40 (2H, m), 2.58 (3H, s), 3.00 (1H, m), 3.40 (2H, m), 4.30 (1H, m), 4.85 (1H, m), 6.20 (1H, m), 7.20-7.40 (5H, m).

LRMS: m/z 468.4 (MH^+)

PREPARATION 11

(1*S*)-3-[*Exo*-3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenyl-1-propanamine



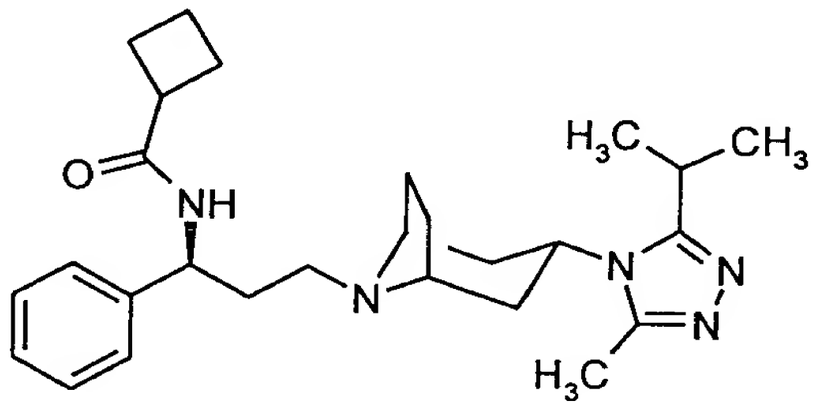
A mixture of the title compound from Preparation 10 (2.5g, 5.35mmol) in a 2.25M solution of hydrochloric acid in methanol (70ml) was heated under reflux for 5 minutes and stirred at room temperature for 1.5 hours. The reaction mixture was allowed to cool to room temperature and evaporated under reduced pressure. The residue was basified by the addition of saturated aqueous sodium carbonate solution (150ml) and extracted with dichloromethane (2x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford the title compound as a white foam, 1.80g.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] 1.37 (6H, m), 1.42 (4H, m), 1.85 (2H, m), 2.05 (2H, m), 2.20 (2H, m), 2.42 (5H, m), 3.00 (1H, m), 3.37 (2H, m), 4.10 (1H, m), 4.30 (1H, m), 7.30 (5H, m).

$[\alpha]_D$ +15.0° (c = 0.10, MeOH)

EXAMPLE 1

N-{(1*S*)-3-[*Exo*-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclobutanecarboxamide



N-Benzyl-N'-cyclohexylcarbodiimide-polymer bound (1.15g, 0.88mmol) was added to a solution of the title compound from Preparation 11 (250mg, 0.68mmol) and cyclobutane carboxylic acid (130µl, 1.37mmol) in dichloromethane (10ml) and the mixture stirred at room temperature for 16 hours. The mixture was filtered through Celite® and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol: 0.88 ammonia (1:0:0 to 95:5:0.5) to afford the title compound as a white foam, 200mg.

Found C, 69.98; H, 8.67; N, 14.89%

$C_{27}H_{39}N_5O$;0.2 CH_2Cl_2; requires C, 70.01; H, 8.51; N, 15.01%

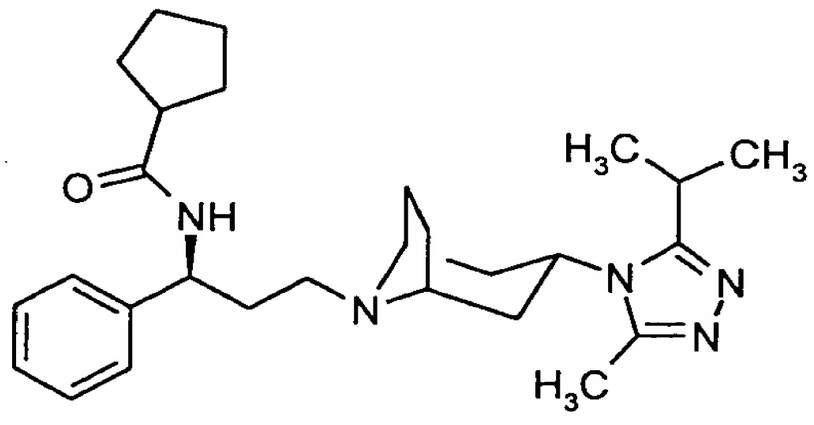
^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] 1.40 (6H, d), 1.63 (4H, m), 1.85-2.45 (14H, m), 2.52 (3H, s), 3.00 (2H, m), 3.39 (2H, m), 4.30 (1H, m), 5.15 (1H, m), 6.35 (1H, m), 7.15-7.40 (5H, m).

LRMS: m/z 450.3 (MH^+)

$[\alpha]_D$ –34.0° (c = 0.10, MeOH)

EXAMPLE 2

N-{(1*S*)-3-[*Exo*-3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclopentanecarboxamide



Cyclopentanecarboxylic acid (115µl, 1.06mmol) was added to a solution of the title compound from Preparation 11 (300mg, 0.82mmol), hydroxybenzotriazole hydrate (10mg, 74µmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide methiodide (300mg, 1.07mmol) in dichloromethane (10ml) and the mixture stirred at room temperature for 3 hours. Saturated aqueous sodium carbonate solution (50ml) was added to the mixture and the product was extracted with dichloromethane (2x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using an elution gradient of dichloromethane: methanol: 0.88 ammonia (1:0:0 to 96:4:0.4) to afford the title compound as a white foam, 330mg.

Found C, 69.73; H, 9.00; N, 14.09%

$C_{28}H_{41}N_5O$; 0.25 CH_2Cl_2; requires C, 69.98; H, 8.63; N, 14.44%.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] 1.35 (6H, d), 1.51-2.04 (16H, m), 2.17 (2H, m), 2.39 (2H, m), 2.45 (4H, m), 2.95 (1H, m), 3.36 (2H, s), 4.25 (1H, m), 5.09 (1H, m), 6.12 (1H, m), 7.20-7.33 (5H, m).

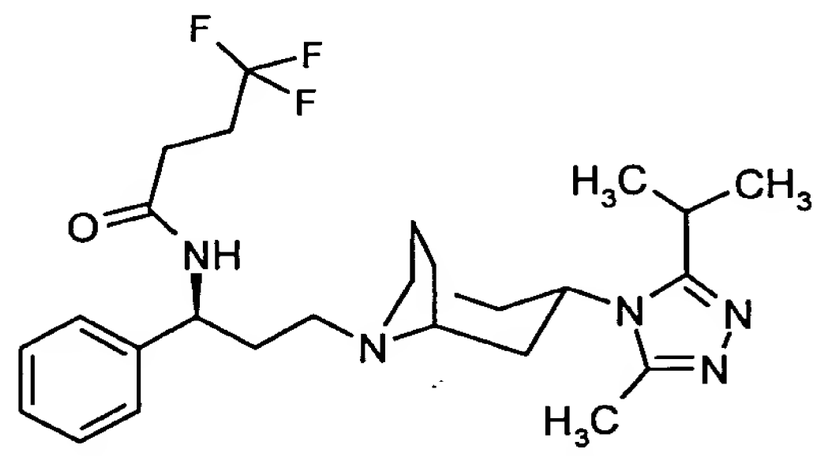
LRMS: m/z 464.8 (MH^+)

$[\alpha]_D$ –29.21° (c = 0.10, MeOH)

Melting point [°C]: 68-70

EXAMPLE 3

N-{(1S)-3-[*Exo*-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}4,4,4-trifluorobutanamide



N-Benzyl-N'-cyclohexylcarbodiimide-polymer bound (370mg, 0.336mmol) was added to a solution of the title compound from Preparation 11 (100mg, 0.27mmol) and 4,4,4-trifluorobutane carboxylic acid (45mg, 0.32mmol) in dichloromethane (4ml) and the mixture was stirred at room temperature for 1.5 hours. The mixture was filtered through Celite® and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using an elution gradient of dichloromethane: methanol: 0.88 ammonia (1:0:0 to 95:5:0.5) to afford the title compound as a white foam, 75mg.

Found C, 61.55; H, 7.46; N, 13.62%

$C_{26}H_{36}N_5OF_3$;0.25 CH_2Cl_2; requires C, 61.48; H, 7.17; N, 13.66%

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] 1.39 (6H, d), 1.65 (5H, m), 1.98 (2H, m), 2.07 (2H, m), 2.15-2.29 (2H, m), 2.43 (5H, m), 2.52 (3H, s), 3.00 (1H, m), 3.40 (2H, s), 4.30 (1H, m), 5.15 (1H, m), 6.94 (1H, m), 7.28 (3H, m), 7.36 (2H, m)

LRMS: m/z 492.3 (MH^+)

$[\alpha]_D$ –32.41° (c = 0.10, MeOH)

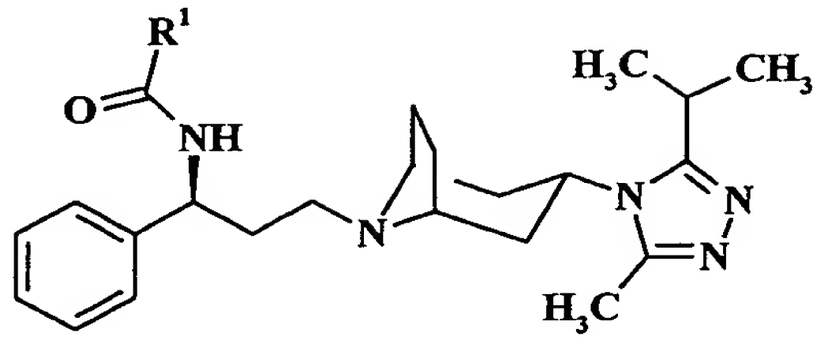
Example 4

Biological activity

The compounds of Examples 1-3 were tested in the assay for CCR5 binding following the procedures disclosed in Combadiere *et al.*, *J. Leukoc. Biol.* **60**, 147-52 (1996) (mentioned above). All of the tested compounds were found to have an IC_{50} value less than 20 nM.

Claims:

1. A compound of formula I,



I

wherein R^1 represents C_{3-6} cycloalkyl, or C_{1-6} alkyl substituted by one or more fluorine atoms;

or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in claim 1, wherein R^1 represents C_{3-6} cycloalkyl.

3. A compound as claimed in claim 2, which is N-{(1*S*)-3-[*Exo*-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclobutanecarboxamide, or a pharmaceutically acceptable salt thereof.

4. A compound as claimed in claim 2, which is *N*-{(1*S*)-3-[*Exo*-3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclopentanecarboxamide, or a pharmaceutically acceptable salt thereof.

5. A compound as claimed in claim 1, wherein R^1 comprises a trifluoromethyl group.

6. A compound as claimed in claim 5, which is N-{(1S)-3-[*Exo*-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}4,4,4-trifluorobutanamide, or a pharmaceutically acceptable salt thereof.

7. A compound as defined in claim 1, for use as a pharmaceutical.

8. A pharmaceutical formulation containing a compound as defined in claim 1, and a pharmaceutically acceptable adjuvant, diluent or carrier.

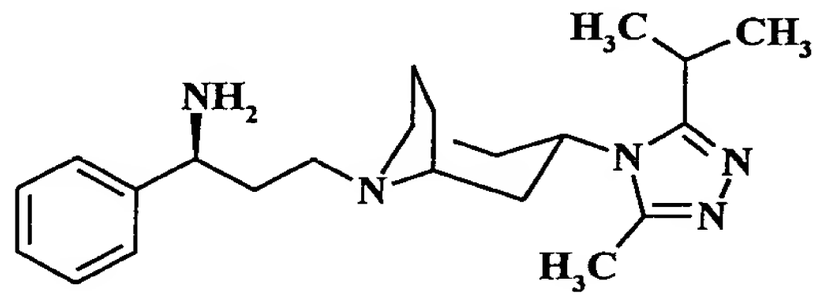
9. Use of a compound as defined in claim 1, in the manufacture of a medicament for the treatment or prevention of a disorder in which the modulation of CCR5 receptors is implicated.

10. Use of a compound as defined in claim 1, in the manufacture of a medicament for the treatment or prevention of HIV, a retroviral infection genetically related to HIV, AIDS, or an inflammatory disease.

11. A method of treatment or prevention of a disorder in which the modulation of CCR5 receptors is implicated, comprising the administration of an effective amount of a compound as defined in claim 1 to a patient in need of such treatment or prevention.

12. A method of treatment or prevention of HIV, a retroviral infection genetically related to HIV, AIDS, or an inflammatory disease, comprising the administration of an effective amount of a compound as defined in claim 1 to a patient in need of such treatment or prevention.

13. A process for the production of a compound as defined in claim 1, which includes: reacting a compound of formula II,



II

with a compound of formula III,

$$R^1CO_2H \qquad \text{III}$$

wherein R^1 is as defined in claim 1;

and where desired or necessary, converting the resulting compound into a pharmaceutically acceptable salt, or vice versa.

14. A compound of formula II, as defined in claim 13.